REMARKS

Claims 1-2, 4-49 are pending in the application, and claims 2, 20, 27, and 41 are withdrawn from consideration, claims 1, 4, 7, 10-12, 17-19, 24, 29-30, 32, 34-35, 39-40, 42-43, and 46-48 have been amended, and new claim 50 has been added. Support for the claim amendments and additions may be found throughout the specification, including the claims as originally filed. No new matter has been added.

Support for the new term "microsphere" in claims 1, 29, 30, 34, 39, 40, 43, 47 and 48 appears at least at specification page 10 lines 26-32, page 11 lines 1-12, page 24 lines 9-20, page 56 lines 28-30 and page 57 lines 1-20 and in original claims 7, 16, 21, 22, 35, 36, 37, 38, 45 and 46.

Support for the new term "polycationic" or "polycation" in claims 1, 11, 12, 29, 30, 35, 39, 40 and 47 appears at least at specification page 18 lines 19-32 and page 56 lines 28-30.

Support for the new term "polyanionic" or "polyanion" in claims 1, 10, 12, 30, 35, 39, 40 and 47 appears at least at specification page 18 lines 19-26, page 19 lines 1-17 and page 56 lines 28-30.

Support for the new term "host" in claims 17, 18 and 19 appears at least at specification page 10 lines 14-17, page 12 lines 1-2, and in original claim 32, 34 and 45.

Support for the new term "bioactive protein" in claim 32 appears at least at specification page 7 lines 1-14.

Support for new claim 50 appears at least at specification page 58 lines 30-31 and page 59 lines 1-9.

Cancellation and/or amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The cancellation and/or amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the right to further prosecute claims drawn to all subject matter disclosed in the instant patent application or in a continuation hereof. The Examiner's remarks in the last Office Action are addressed below. It is believed that the amended claims, taken in light of the remarks made herein, meet all criteria for patentability. Nonetheless, for the Examiner's convenience, we briefly discuss in turn each of the rejections set out in the July 2, 2002 Office Action.

Rejection of claims under 35 U.S.C 112, first paragraph

The Examiner maintained the rejection under 35 U.S.C. 112, 1st paragraph of the following claims: "32 (when read as a whole encompassing claims 30, 31), 34, 39, 17-20 (when read as a whole encompassing claims 15, 4, 2, 1) and 22 ". The Examiner maintained that it would require undue experimentation to practice the claimed methods of gene therapy and nucleic acid immunization. Applicants respectfully traverse this rejection.

The Examiner acknowledged that the specification discloses and supports "the preparation of microspheres made by the coacervation of gelatin and alginate in the presence of recombinant adenovirus containing a luciferase expression cassette". The Examiner further acknowledges that the Applicants have demonstrated that "bioactive adenovirus was released *in vivo* from the microspheres that were injected intratumorally, as evident by the luciferase activity in harvested tumor nodules". The Applicants respectfully assert that the specification provides adequate support for the delivery of a bioactive adenovirus encoding a bioactive protein to target cells and tissues in a host via coacervate microspheres and the successful expression of a bioactive protein in target cells and tissues in a host. The amended claims conform fully to the scope of disclosure in the application. Thus, in light of the Examiner's remarks, Applicants believe that the present amendments are sufficient to obviate the rejection.

The Examiner further rejected the nucleic acid immunization methods recited in claims 20 and 27. Claims 20 and 27 are herein cancelled without prejudice, rendering the instant rejection moot. Applicants reserve the right to further prosecute the subject matter of these claims in this or a subsequent related patent application.

With respect to the claimed methods of gene therapy, Applicants believe that the claims herein are fully in accord with the support provided within the specification. Claims 17, 18, and 19 have been amended to recite "host" in lieu of "patient" to address and overcome Examiner's rejection. Claim 32 has been amended to recite "bioactive protein" in lieu of "therapeutic agent".

Applicants respectfully submit that the claim amendments made herein fully overcome and obviate the stated grounds for rejection of said claims. Applicants urge the Examiner to reconsider and withdraw the rejections under 35 U.S.C. 112, 1st paragraph.

Claims 1-2, 4-10, 13-16, 21, 23-31, 33, 35, and 40-49 remain rejected by the Examiner under 35 U.S.C. 112, 1st paragraph, for over breath for reasons stated in the Office Action at

pages 12 and 13. The Examiner points out "the specification, while being enabling for a composition for controlled release of a nucleic acid comprising a coacervate microsphere encapsulates a nucleic acid associated with a delivery agent, wherein the coacervate microsphere comprises a polycation molecule and a polyanion molecule..." Applicants have amended the claims in accordance with the terms used by the Examiner. It is believed that the present rejection has been obviated.

Applicants respectfully request reconsideration and withdrawal of all rejections under 35 U.S.C. 112, insofar these may apply to the amended claims. It is believed that the amended claims comply fully with 35 USC 112, first paragraph thus favorable reconsideration and allowance are respectfully solicited.

Rejection of claims under 35 U.S.C 103(a)

The Examiner maintained the rejection of amended claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al. (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997). Applicants traverse this rejection.

Russell-Jones et al. (US 6,159,502) describes a microparticle or microsphere system for oral delivery of substances which would otherwise be degraded within the gastrointestinal tract. Specifically, the Russell-Jones microparticles rely on the use of a carrier defined as "including mucosal binding proteins, Vitamin B12, and analogues or derivatives of Vitamin B12 possessing binding activity to Castle's intrinsic factor." (col. 4, lines 34-37). Issued claims 1-15 recite microparticle complexes, processes for making the complexes, kits, and compositions that are physiologically acceptable for oral administration, all of which include as a carrier component Vitamin B12 or a Vitamin B12 analogue that binds Castle's intrinsic factor (a gastrointestinal receptor which mediates Vitamin B12 uptake). By virtue of this carrier, the microparticles, when administered (i.e., ingested) are transported across the gut lining and delivered "to the circulation or lymphatic drainage system of the host." (see, e.g., claim 1 and col. 2, lines 5-11; col. 3, lines 5-8; col 4, lines 13-16; col. 5, lines 26-30; col. 9, lines 40-49; col. 12, lines 32-36). In other words, the microparticles are delivered systemically to the host -- not locally to any specific tissue (col. 2, line 11; col. 5, lines 24-26; col. 9, lines 40-49).

It is noted that, at col. 5, lines 30-38, Russell-Jones briefly discusses the possibility of including a targeting molecule "which [can] target and attach the [microparticles] to or in the vicinity of a desirable target in the host (.e., an organ in the host)". However, this element is present optionally in addition to the carrier molecule which promotes the transport of the microparticle across the intestinal lining. Nowhere does Russell-Jones teach or suggest the omission of the carrier molecule. In fact, the entire specification emphasizes that it is the carrier molecule which sets the invention apart and defines it as an advance over the state of the art. The Examiner's attention is directed to col. 3, line 58 - col. 4, line 16: the inventors urge that, surprisingly, due to the carrier molecule, it is now possible to orally administer a relatively large microparticle, to have the microparticle transported via the mucosal epithelium of the host, thereby to have the microparticle (and its encapsulated substance) delivered to the circulatory or lymphatic drainage system of the host.

In contrast, the present invention as recited in the claims amended herein lacks any element which corresponds to the carrier of Russell-Jones. The instant claimed invention contemplates coacervate microspheres, and methods of making and using the same, that may be used to deliver bioactive substances. In certain embodiments, a delivery agent may be encapsulated in the coacervate to facilitate the intracellular delivery of any bioactive substance. As defined in the specification (line 5-13, page 9 and page 27-32), the term "delivery agent" may include: sterols, lipids, viruses, or target cell binding agents (e.g. ligands recognized by target cell specific receptors). In certain embodiments wherein the bioactive substance is a nucleic acid, the delivery agent comprises a virus or a virus particle engineered to contain the nucleic acid. As contemplated by the Applicants, the virus may be recombinant retrovirus, adenovirus, adeno-associated virus, herpes simplex virus-1, vaccinia virus and RNA viruses.

In order to render a claimed invention obvious, the teachings of a prior art reference must disclose all elements of the invention or must suggest to, or motivate, the skilled person to modify the reference teachings so as to arrive at the claimed invention, including all of its elements. The suggestion or motivation must be found in the prior art. Here, Applicants urge that the Russell-Jones reference fails to motivate or suggest to the skilled person that the microparticles disclosed therein should be modified by omission of the carrier molecule. Indeed, by emphasizing the importance of the carrier, Russell-Jones discourages such modification. Furthermore, Russell-Jones fails to provide any guidance beyond a general suggestion, i.e., an

invitation to experiment, regarding the inclusion of a delivery molecule for targeting the microspheres to any specific tissue.

We accordingly reviewed the Beer reference to learn whether it contains any suggestion or motivation sufficient to overcome the disincentive for omitting the carrier molecule from the microparticles of Russell-Jones. We additionally considered whether Beer et al. provide any specific guidance or direction for incorporating any targeting molecules in the microparticles. Beer et al. (1997), 27 Advanced Drug Delivery Reviews 59-66, report the results of preliminary experiments on the microencapsulation of recombinant adenovirus using PGLA (poly lactic-glycolic acid). (p. 63, col. 2, lines 10-12). The procedure for microencapsulation is set out at page 61 (col. 1, line 17 to col. 2, line 9). As the Examiner has pointed out, at page 63, lines 42-44, Beer et al. suggest that "different polymers should be investigated for their ability to allow for sustained release of recombinant viral vectors." However, the Beer reference fails to teach or suggest that coacervate microspheres in particular should evaluated as potential encapsulation systems for viral or other nucleic acid vectors. We also note that Beer et al. injected their microsphere preparation directly into the striata of mice (page 63, col. 1, lines 15-18). This technique stands in contrast to the Russell-Jones technique of oral administration for systemic uptake into the circulation and/or lymphatic drainage system of the host. Only in this respect of localized administration does Beer et al. provide any teachings or guidance for targeting the encapsulated virus to any specific tissue. No molecular components for accomplishing this task are disclosed or suggested.

Accordingly, the combined teachings of Russell-Jones and Beer are devoid of any teaching, suggestion, motivation, or guidance for modifying any microparticle of the prior art (including coacervate microspheres) so as to include a nucleic acid and a delivery agent for targeting the nucleic acid to a desired tissue within the host. Applicants respectfully submit that the claimed invention cannot be deemed obvious in light of the combined teachings of these two references. The first rejection under 35 U.S.C. 103(a) (Office Action pages 13-18) should be reconsidered and withdrawn.

Insofar as the second, third, and fourth rejections under 35 U.S.C. 103(a) rely on Russell-Jones, alone or in combination with Beer et al. and other references (Office Action pages 18-27), Applicants submit that each such rejection is defective and should be reconsidered and withdrawn in light of the foregoing discussion. Nonetheless, Applicants briefly discuss each of

the additional cited references below, explaining why each fails to remedy the defects of Russell-Jones, whether taken alone or in combination with Beer.

The Examiner stated that "[c]laims 40-47 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al (U.S. Patent No. 6,159,502) in view of Beer et al. (Adv. Drug Delivery Reviews 27:59-66, 1997) as applied to claims 1-2, 4-5, 10-20, 23-31, 33-39 and 48 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582).

Leong et al. (U.S. 5,759,582) describe the preparation of coacervate microspheres and their use to encapsulate pharmaceutically active substances. (col. 4, lines 48-67). We note that, in the list of pharmaceutically active substances disclosed at col. 3, lines 12-32, Leong et al. define "pharmaceutically active substances" and provide a detailed list of substances considered to be pharmaceutically active. Nucleic acids in general, and viruses in particular, are conspicuously absent from this list. Moreover, Leong et al. provides no teachings or guidance for targeting the microspheres to any specific body tissue, other than by direct local injection (e.g., col. 5, lines 21-24). This reference fails to teach or suggest any molecular component for use as a delivery agent to target the microspheres.

The Leong reference does not provide any incentive, motivation, or guidance for overcoming the Russell-Jones disincentive for omitting a carrier molecule and/or for including a molecular delivery agent so that the microspheres can be targeted to a specific body tissue. Accordingly, Leong et al. fails to remedy the defects noted above with respect to the Russell-Jones and Beer combination. The second rejection under 35 U.S.C. 103(a) (Office Action pages 18-21) is insufficient to render the claimed invention obvious. Applicants respectfully submit that this rejection should be reconsidered and withdrawn.

The Examiner maintained that "[a]mended claims 1-6, 10-15, 17, 22 and 49 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Russell-Jones et al (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738).

McElligott et al. (WO 94/23738) teaches the microencapsulation of nucleic acids, wherein the nucleic acid is conjugated chemically to a promoting material that promotes uptake into cells, transport to the cell nucleus, or expression of nucleic acid in the cell. (e.g., claim 1). Although numerous encapsulation methodologies are disclosed at pages 15-27, coacervation is not mentioned. Further, as has been discussed previously, the promoting material is conjugated

directly to the nucleic acid by covalent bonds (pages 12-15) or the formation of salt bridges (page 14).

The McElligott reference does not provide any incentive, motivation, or guidance for overcoming the Russell-Jones disincentive for omitting a carrier molecule from the microspheres. Accordingly, McElligott et al. fails to remedy the defects noted above with respect to Russell-Jones. Moreover, one following the techniques of McElligott would believe that a delivery agent or promoting material for facilitating intracellular delivery would have to be covalently conjugated to the nucleic acid, which Applicants have shown is not the case. The third rejection under 35 U.S.C. 103(a) (Office Action pages 21-25) is insufficient to render the claimed invention obvious. Applicants respectfully submit that this rejection should be reconsidered and withdrawn.

The Examiner also maintained the rejection of amended claims 1, 2 and 7-9 as being "unpatentable over Russell-Jones et al (U.S. Patent No. 6,159,502) in view of McElligott et al. (WO 94/23738) as applied to claims 1-6, 10-15, 17, 22, and 49 above, and further in view of Leong et al. (U.S. Patent No. 5,759,582) and Gombotz et al. (U.S. Patent No. 5,942,253).

Gombotz et al. (U.S. 5,942,253) teaches the production of microparticle encapsulated GM-CSF. Numerous techniques are described at col. 3 to col. 9 for the formation of microspheres from a variety of different polymer materials. However, coacervate formation is not discussed. At col. 6, lines 14-40, the Gombotz reference teaches the use of divalent and trivalent cations such as calcium to crosslink hydrogel forming polymers. There is no indication of whether such a technique would be beneficial or even necessary for the production of coacervate microspheres.

The combined teachings of Russell-Jones and McElligott have been discussed above and distinguished from the claimed invention. Applicants urge that neither Leong nor Gombotz remedies the defects of the Russell-Jones / McElligott combination. Neither one provides any guidance, motivation, or suggestion that overcomes the Russell-Jones teachings that a carrier molecule should be included. Moreover, in addition to including a carrier molecule, any microparticle based on the combined teachings of Russell-Jones and McElligott would include a promoting material that is actually conjugated to the encapsulated nucleic acid. Whereas Gombotz et al. teach the option of crosslinking hydrogel polymers, neither this reference nor Leong et al. teach or suggest that it would be beneficial to do so in the case of coacervates. Each

of the foregoing reasons illustrates why the combination proposed by the Examiner at Office Action pages 26-27 is insufficient to render the claimed invention obvious. Applicants respectfully submit that the fourth rejection under 35 U.S.C. 103(a) should be reconsidered and withdrawn.

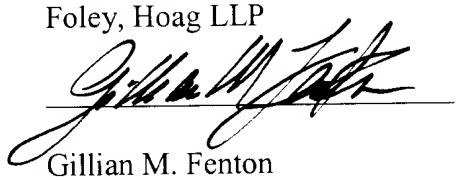
In conclusion, Applicants have explained why each grounds for rejection under Section 103(a) fails to render the claimed invention obvious, and have asked that each rejection should be reconsidered and withdrawn. It is believed that the application, as amended herein, is free of the cited art of record.

Summary

Applicants have, by way of the amendments and remarks made herein, obviated or rendered moot each of the rejections set forth in the July 2, 2002 Office Action. Applicants respectfully urge that the amended application is in condition for allowance. Favorable reconsideration and early allowance thereof are respectfully solicited.

If the Examiner has any questions, or believes that a teleconference would facilitate the further prosecution of this application, the Examiner is urged to contact the undersigned at the telephone number listed below.

Respectfully submitted,
Foley, Hoag LLP

By: 

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MARK UP SHOWING AMENDMENTS TO THE CLAIMS

1. **(Newly amended)** A composition for controlled release of a nucleic acid, comprising:

a. a coacervate microsphere;

b. a nucleic acid incorporated in said coacervate microsphere; and

c. a delivery agent incorporated in said coacervate microsphere,

wherein the coacervate microsphere comprises a polycationic molecule and ~~a~~n polyanionic molecule other than said nucleic acid and the delivery agent is other than said polycationic molecule of the coacervate microsphere.

2. **(Canceled)**

4. **(Newly amended)** The composition of claim ~~2~~ 1, wherein said nucleic acid is a transfer vector.

5. The composition of claim 4, wherein said transfer vector includes a transgene.

6. The composition of claim 4, wherein said delivery agent is at least one of the following: amphiphilic molecule, lipid or polylysine.

7. **(Newly amended)** The composition of claim ~~2~~ 1, wherein said microsphere is crosslinked by a crosslinking agent.

8. **(Previously amended)** The composition of claim 7, wherein said crosslinking agent comprises a metal cation.

9. The composition of claim 8, wherein said metal cation comprises calcium.

10. **(Newly amended)** The composition of claim 1, wherein said polyanionic molecule is alginate.

11. **(Newly amended)** The composition of claim 1, wherein said polycationic molecule is gelatin.

12. **(Newly amended)** The composition of claim 1, wherein said polycationic molecule is gelatin, and wherein said polyanionic molecule is alginate.

13. The composition of claim 4, wherein said transfer vector comprises at least one regulatory element.

14. The composition of claim 13, wherein said regulatory element is a promoter.

15. The composition of claim 4, wherein said transfer vector comprises an expression vector.

16. The composition of claim 4, wherein said transfer vector comprises a viral vector, said delivery agent is a virus, and said virus comprises at least about five percent by weight of said microsphere.

17. **(Newly amended)** The composition of claim 15, wherein said microsphere, when administered to a ~~patient~~ host, provides controlled release of said expression vector.

18. **(Newly amended)** The composition of claim 17, wherein said delivery agent facilitates intracellular delivery of said expression vector in said ~~patient~~ host.

19. **(Newly amended)** The composition of claim 18, wherein said expression vector produces a recombinant protein in said ~~patient~~ host.

20. **(Canceled)**

21. The composition of claim 4, wherein said microsphere is lyophilized.

22. The composition of claim 17, wherein said microsphere further comprises a second expression vector.

23. The composition of claim 1, wherein said nucleic acid is a viral vector, and said delivery agent is a virus.

24. **(Newly amended)** The composition of claim ~~2~~ 1, wherein said delivery agent is a virus of said a viral vector.

25. The composition of claim 24, wherein said viral vector contains a transgene.

26. **(Previously amended)** The composition of claim 24, wherein said viral vector contains a nucleic acid encoding a recombinant gene product.

27. **(Canceled)**

28. The composition of claim 24, wherein said viral vector and said virus of said viral vector are one of the following: recombinant retrovirus, adenovirus, adeno-associated virus, or herpes simplex virus-1.

29. **(Newly amended)** A gene delivery system for transducing cells, comprising: a coacervate microsphere encapsulating at least a nucleic acid and a delivery agent that is other than a polycation of the coacervate microsphere, for facilitating intracellular delivery of said nucleic acid, wherein upon contact of cells with said coacervate microsphere, controlled release of said nucleic acid results in transduction of the cells by said nucleic acid.

30. **(Newly amended)** A method for delivering a nucleic acid into a cell, comprising: contacting a cell with a composition comprising a coacervate microsphere, wherein:

i. said coacervate microsphere incorporates a nucleic acid contained in a transfer vector having at least one regulatory element:

ii. said coacervate microsphere comprises a polycationic molecule and ~~a~~n polyanionic molecule other than said nucleic acid; and,

~~iii. said coacervate is a microsphere; and.~~

~~iv~~ iii. said coacervate incorporates a delivery agent,

wherein said contacting of a cell with said composition results in controlled release of said transfer vector in the cell.

31. The method of claim 30, wherein said transfer vector is a viral vector, said delivery agent is a virus of said viral vector, and said viral vector is enveloped in said virus.

32. **(Newly amended)** The method of claim 31, wherein the nucleic acid encodes a bioactive protein ~~therapeutic agent~~, the cell is in a host and is transfected with the nucleic acid and expresses the bioactive protein ~~therapeutic agent, and said agent produces a therapeutically beneficial response in said host~~.

33. The method of claim 31, wherein said virus facilitates intracellular delivery of said viral vector.

34. **(Newly amended)** The method of claim 31, further comprising administering said coacervate microsphere as a pharmaceutical composition to a host.

35. **(Newly amended)** A kit containing a gene delivery system, comprising microspheres and instructions for using said microspheres, wherein said microspheres are comprised of a polycationic molecule and a~~n~~ polyanionic molecule and said microspheres encapsulate a virus.

36. A coacervate microsphere for sustained release of a virus, comprising: a coacervate of gelatin and alginate having a virus incorporated therein.

37. **(Previously amended)** The coacervate microsphere of claim 36, wherein said virus comprises a recombinant virus.

38. A method for the sustained release of a virus to a target site, comprising: providing to the target site a coacervate microsphere comprising a coacervate of gelatin and alginate having a virus incorporated therein.

39. **(Newly amended)** A method for preparing a pharmaceutical preparation, comprising combining a pharmaceutically acceptable excipient with a coacervate microsphere of polycationic and polyanionic molecules, wherein a recombinant virus is encapsulated in said coacervate microsphere.

40. **(Newly amended)** A method for preparing a gene delivery system, comprising:

a. preparing a first solution of ~~a~~ polycationic molecules and a second solution of ~~an~~ polyanionic molecules;

b. adding to either said first solution or said second solution a nucleic acid; and adding to either said first solution or said second solution a delivery agent;

c. combining said first solution and said second solution to form a third solution comprising the nucleic acid and the delivery agent; and,

d. isolating coacervates microspheres formed from a portion of said polycationic molecules and a portion of said polyanionic molecules from said third solution,

wherein said coacervates microspheres encapsulate at least a portion of said nucleic acid and said delivery agent.

41. **(Canceled)**

42. **(Newly amended)** The method of claim ~~41~~ 40, wherein said delivery agent comprises a virus particle including said nucleic acid.

43. **(Newly amended)** The method of claim ~~41~~ 40, further comprising mixing said third solution to form said coacervates microspheres.

44. The method of claim 42, wherein said first and said second solution are substantially aqueous.

45. The method of claim 42, further comprising preparing said microspheres for administration to a host, wherein preparing said microspheres does not impair the controlled release of said virus particle from said microspheres.

46. **(Newly amended)** The method of claim ~~41~~ 40, further comprising lyophilizing said microspheres after said isolation.

47. **(Newly amended)** A coacervate microsphere for transfection and expression of a recombinant protein prepared by the process comprising:

a. in any order:

i. adding a polycationic molecule to a first aqueous solution;

ii. adding a polyanionic molecule to a second aqueous solution; and,

iii. adding to either said first or said second solution a virus comprising a viral vector comprising a nucleic acid encoding a recombinant protein and at least one regulatory element;

b. mixing said first and second solution together to form a coacervate microsphere of said polycationic molecule and said polyanionic molecule encapsulating said virus; and,

c. isolating said coacervate microspheres.

wherein said coacervate microsphere releases said virus in vivo or in vitro, whereby said virus transfects cells, resulting in expression of said recombinant protein.

48. **(Newly amended)** A gene delivery system for transfecting a cell with a viral vector, comprising:

a. encapsulation means for encapsulating a viral vector;

b. delivery means for facilitating intracellular delivery of said encapsulated viral vector;

wherein said encapsulation means comprises a coacervate microsphere, and wherein release of said encapsulated viral vector from said encapsulation means transfects a cell.

49. The composition of claim 1, wherein the nucleic acid encodes a polypeptide which inhibits cell proliferation.

50. **(New)** A method for the sustained release of a virus to a cancer cell, comprising providing to the target site, a coacervate microsphere comprising a coacervate of gelatin and alginate having a virus incorporated therein.